REMARKS

Applicants acknowledge the current status of the claims, as reported in Office Action dated 17 August 2006: Claims 4-8, 11-88 and 96-104 are pending; claims 5-8, 11, and 32-88 are withdrawn from consideration; claims 4, 12-30 are allowable; claims 31, and 96-104 stand rejected.

As a matter of formality, Applicants make note of a typographical error occurring in the Office Action Summary, wherein the status of claim 4 is not reported. The full status of the claims are correctly stated in the Detailed Action of the Office Action dated 17 August 2006, at page 2, paragraph 1.

Applicants acknowledge the Examiner's withdrawal of finality of the previous Office Action.

Applicants acknowledge, with traverse, the Examiner's withdrawal of allowability of claim 31.

Reconsideration and allowance of the pending claims in light of the foregoing amendment and following remarks are respectfully requested.

Claim 31 is hereby canceled without prejudice to advance examination of the present application to allowance. Applicants reserve the right to prosecute canceled subject matter in a later-filed continuation application, which properly claims the benefit of this application.

Rejections under 35 USC §103(a)

In the Office Action, starting at page 2, paragraph 4, rejection of claims 96-104 under 35 USC §103(a) are maintained as being unpatentable over Luger et. al., Immunobiology, 1986, vol. 172, pp. 346-356 in view of Schmidt et. al., (EP0218531) and Berg (US Patent 5622701). The Examiner asserts "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a dual specificity antibody with enhanced sensitivity against both IL-1α and IL-1β." Specifically, the Examiner relies on the disclosure of Schmidt et al. to conclude "The ten amino acid sequence peptide of Schmidt et al., combined with the sequence overlap with the four amino acids that are potential antigenic epitopes of both IL-1α and IL-1 β is sufficient to permit antibodies raised against the peptide of Schmidt et al., to be used to bind both IL- 1α and IL-1β." Applicants respectfully disagree.

Applicants continue to assert and to rely on the three basic criteria that must be met to establish a *prima facie* case of obviousness:

1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

2) there must be a reasonable expectation of success, and

3) the prior art reference (or references when combined) must teach or suggest all claim limitations.

(MPEP §2143).

Previously, Applicants have asserted that the present rejection fails to establish a proper *prima facie* case of obviousness because the cited art, neither singularly, nor in combination, provide teaching suggestion, or motivation the present invention: the first of the above-enumerated criteria that must be met to establish a *prima facie* case of obviousness. The present Action holds that such arguments have been fully considered, but found not persuasive.

Without restating Applicants' rebuttal on record to the rejections based upon on these arguments, Applicants maintain their position that there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings to create Applicants' claimed antibody, or antigen-binding portion thereof (including Applicants' dependent claim embodiments of fully human, chimeric, CDR-grafted, and humanized antibody), that specifically binds IL-1α and IL-1β, wherein the antibody (or antigen-binding portion thereof) is capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ (SEQ ID NO: 3). Instead, the Examiner has applied impermissible hindsight, in an effort to reconstruct Applicant's present invention.

Applicants further assert that rejection of claims 96-104 under 35 USC §103(a) as obvious is improper because the cited art references fail to teach or to suggest all claim limitations: the third of the above-enumerated criteria that must be met to establish a *prima facie* case of obviousness.

Applicants further assert that rejection of claims 96-104 under 35 USC §103(a) as obvious is improper because there is no a reasonable expectation of success: the second of the above-enumerated criteria that must be met to establish a *prima facie* case of obviousness.

Claim 96 is directed to a dual-specificity antibody, or antigen binding portion thereof, that;

i) specifically binds interleukin-1α and interleukin-1β, wherein said dual-specificity antibody, or antigen-binding portion

ii) is capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ (SEQ ID NO: 3)

Claims 97-104 recite further specific embodiments of Applicants' invention wherein Applicants' dual-specificity antibody is; a fully human antibody (claim 98), a chimeric antibody (claim 99), a CDR grafted antibody (claim 101) or a humanized antibody (claim 104).

Luger et al. disclose a mouse monoclonal antibody that cross-reacts with IL-1α and IL-1β. Luger et al. do not teach (as previously acknowledged by the Examiner) an antibody, or antigen binding portion thereof, capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ.

Schmidt et al. disclose peptides derived from IL-1β and antibodies to those peptides. Specifically, Schmidt et al. disclose an antibody to the amino acid sequence THR LYS GLY GLY GLN ASP ILE THR ASP PHE THR (i.e., TKGGQDITDFT) (Claim 1, page 11, line 2). Schmidt et al. do not teach or suggest an antibody, or antigen binding portion thereof, capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ.

Berg discloses monoclonal antibodies capable of binding P-Selectin and E-Selectin. Berg does not teach or suggests an antibody, or antigen binding portion thereof, capable of binding IL-1α and IL-1β. Berg does not teach or suggests an antibody capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ.

Cited art must teach or suggest all claim limitations

The "all-elements" requirement for obviousness is a bright line test. It is well-settled that all elements of a claim must be present to establish a proper *prima facie* case of obviousness. Separate and independent from the other two essential criteria for establishing a *prima facie* case of obviousness, there is no, "motivation", "modification", or "reasonable expectation" component to the all elements criterion for establishing *prima facie* obviousness; ALL claim limitations must be taught or suggested in the cited art (MPEP 2143.03).

Applicants assert that none of the cited art, singularly, or in combination, teach or suggest all claim limitations. For example, Luger et al., Schmidt et al., and Berg all fail to teach or to suggest the explicitly recited feature of Applicants' claimed antibody that it is "capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ(SEQ ID NO: 3)."

The Examiner relies on the disclosure of Schmidt et al., citing the feature that one of the disclosed peptides of Schmidt et al. (i.e, TKGGQDITDFT) shares a ten amino acid sequence in common with the sequence recited in Applicant's claimed invention (i.e, TKGGQDITDFQILENQ).

The disclosed peptide of Schmidt et al. is not the peptide recited in Applicants' claimed invention. Not only is the antigenic sequence of Applicants' invention significantly longer than that disclosed by Schmidt et al., the recited amino acid sequences of the two polypeptides are, in fact, different in their amino acid sequence. Amino acid sequence defines the primary structure of a polypeptide. Polypeptides of different amino acid sequence are, in fact, structurally different. Schmidt et

al. fails to provide the antigenic binding feature of Applicants claimed antibody in satisfaction of the all elements requirement to establish a *prima facie* case of obviousness.

The Examiner asserts that "The ten amino acid sequence peptide of Schmidt et al., combined with the sequence overlap with the four amino acids that are potential antigenic epitopes of both IL-lα and IL-l β is sufficient to permit antibodies raised against the peptide of Schmidt et al., to be used to bind both IL- lα and IL-1β." Applicants respectfully disagree.

As an initial matter, the cited Schmidt et al. peptide sequence is not a "ten amino acid sequence peptide" as asserted by the Examiner. The Schmidt et al. peptide is an eleven amino acid peptide, whose primary sequence structure is different from that of Applicants' antigenic peptide. The Examiner has improperly characterized the disclosed Schmidt et al. peptide sequence in an effort to "deconstruct" the Schmidt et al. peptide (modification by amino acid residue truncation), and then to "reconstruct" a peptide (modification by amino acid residue additions) into Applicant's recited antigenic peptide.

Notwithstanding the above, and by the Examiner's own admission, the deconstructed Schmidt et al. peptide is "**combined** with the sequence overlap with the four amino acids that are **potential** antigenic epitopes' of both IL-lα and IL-l β" (emphasis added). Applicants' assert that such modification and "combination" with a four amino acid sequence, not taught or suggested in the cited art is improper. In addition, the improperly reconstructed peptide, having a "potential" to be antigenic, is nothing more than speculation (absent Applicants' specification) on the part of the Examiner, and as such is improper.

Because the cited prior art fails to teach or to suggest Applicants' claimed antibody "capable of binding an antigen comprising the amino acid sequence TKGGQDITDFQILENQ(SEQ ID NO: 3), as an element of Applicants' claimed invention, the present rejection fails to satisfy the all elements criterion that a *prima facie* case of obviousness must satisfy.

There must be a reasonable expectation of success

While a *prima facie* case of obviousness does not require absolute predictability, a reasonable degree of predictability (determined at the time the invention was made) is required (MPEP 2143.02).

As stated, the Examiner asserts "The ten amino acid sequence peptide of Schmidt et al., combined with the sequence overlap with the four amino acids that are **potential** antigenic epitopes of both IL-lα and IL-l β is **sufficient to permit antibodies raised against the peptide** of Schmidt et al., to be used **to bind both IL- lα and IL-1β**." (emphasis added).

Applicants have rebutted, *supra*, that the Examiner has improperly characterized the Schmidt et al. peptide, as a ten amino acid peptide, when, in fact, the eleven amino acid peptide disclosed by Schmidt et al. is structurally different than the sixteen amino acid antigen recited in Applicants' claimed

invention, thereby failing to satisfy the all elements criterion for establishing a *prima facie* case for obviousness.

In addition, Applicants argue that the Examiner has improperly speculated that the hypothetically deconstructed & reconstructed peptide of the Examiner's rejection; i) is antigenic (i.e., capable of eliciting an immune response in an animal) and ii) an antibody, or antigen binding portion thereof, raised against such a peptide would further specifically bind interleukin-1α and interleukin-1β.

It is the Applicant's position that in the absence of the present disclosure, both of these suppositions are unpredictable. Applicants need look no further than the history of the present application prosecution in support of this position.

In the Office Action, date 02 August 2004, at page 11, the Examiner rejected Applicants' then-pending claims to dual-specificity antibodies generated to "an antigen, that comprises a common structural feature of IL-1α and IL-1β" under 35 USC §112, as not enabling. The rejection then stated:

> "[T]he essential characteristics of peptides able to generate dual specificity antibodies are not described. Further, it is not routine in the art to screen large numbers of peptides that might **potentially generate** such antibodies where **the expectation of obtaining similar specificity is unpredictable. The prior art does not provide compensatory teachings**;"
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> (Office Action, date 02 August 2004, at page 12; emphasis added).

Again, by the Office's own admission (and in opposition to the present argument of rejection), the potential of a peptide; i) to generate an antibody, and ii) of such antibody to specifically bind other antigens is unpredictable. Further, it is stated, of record, that the "prior art" does not provide adequate teachings. A *prima facie* case of obviousness requires a reasonable expectation of success. A reasonable expectation of success requires some degree of predictability. Without some degree of predictability, there is no reasonable expectation of success. Without a reasonable expectation of success, a *prima facie* case of obviousness must fail. The United States Patent Office should not be permitted to vacillate in its arguments on the adequacy of teachings in the art to suit situational rejections.

Because the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 96-104 as obvious under 35 USC §103(a), and in view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 96-104 under 35 USC §103(a).

In the present Office Action, at page 4, paragraph 6, claim 31 is newly-rejected under 35 USC §103(a) as being unpatentable over Luger et. al., Immunobiology, 1986, vol. 172, pp. 346-356 in view of Schmidt et. al., (EP0218531) and Berg (US Patent 5622701).

Applicants have hereby canceled claim 31, without prejudice, to advance examination of the present application to allowance. Applicants reserve the right to prosecute canceled subject matter in a later-filed continuation application, which properly claims the benefit of this application. In view of claim 31 being canceled, the present rejection is rendered moot. Applicants respectfully request removal of the rejection of claim 31 under 35 USC §103(a).

Conclusion

In view of the foregoing amendment and remarks, Applicants believe that all objections and rejections set forth in the Office Action of 17 August 2006 have been obviated or overcome, and consequently the application is in condition for allowance. Reconsideration, withdrawal, and removal of the rejections, and allowance of the pending amended claims are, therefore, respectfully requested.

Respectfully submitted,

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